Synergistic Copper/Palladium Catalysis for the Regio- and Stereoselective Synthesis of Borylated Skipped Dienes

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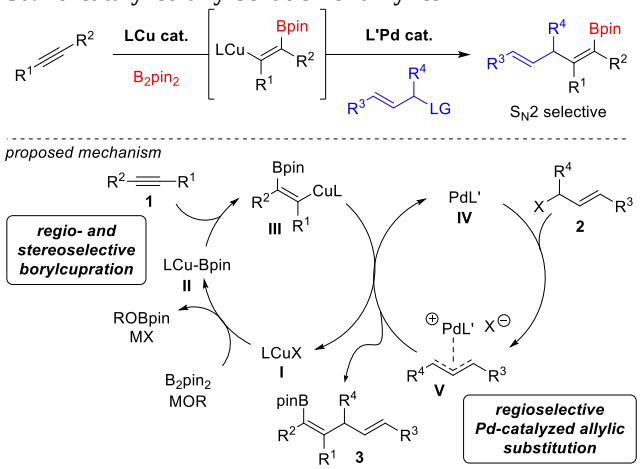
ABSTRACT: A Cu/Pd-catalyzed allylboration of alkynes with allyl carbonates and bis(pinacolato)diboron to afford borylated skipped dienes is reported. Synergistic Cu and Pd catalysis enables this protocol to work for a wide array of alkynes and allyl carbonates under mild conditions with total regio- and stereocontrol. This transformation features the catalytic generation of β-borylalkenylcopper intermediates and their use in Pd-catalyzed allylic substitution of allyl carbonates. The utility of this method is highlighted by the synthesis of (*Z*,*E*)-α-homofarnesene (pheromone) and the terpenoid precursor of Merochlorins (potent antibiotic agents).

KEYWORDS: Synergistic catalysis, copper, palladium, multicomponent reactions, skipped dienes

1,4-Dienes, so called skipped dienes, are common structural motifs in numerous biologically active natural compounds in which the stereochemical identity of the diene unit imparts unique properties.[1] Consequently, general methods that allow for the efficient and stereoselective preparation of skipped dienes are in high demand. Among the catalytic methodologies available for the synthesis of these important molecules,[2] transition metal-catalyzed allylic substitution using alkenylmetal reagents has become a powerful tool.[3-5] Great advance has been made in this field and nowadays selective protocols based on palladium,[3] copper[4] and iridium[5] catalysis are available. However, these methodologies involve the preparation and use of stoichiometric amounts of basic alkenylmetal reagents. The high reactivity of most of these organometallic reagents imposes limitations with respect to the functional-group tolerance and examples involving the use of functionalized alkenylmetal reagents are scarce.[4e] In this context, a catalytic method for stereoselective allylic substitution using simple alkynes as transient functionalized alkenylmetal species would circumvent these issues and greatly expand the scope of stereodefined skipped dienes.

Borylcopper complexes can add across an alkyne to generate nucleophilic β-borylalkenylcopper species.[6] These organocopper intermediates can react in a catalytic fashion by protonation with alcohols to afford formal hydroboration products[7] or with carbon electrophiles in carboboration reactions.[8-12] To develop a regio- and stereoselective catalytic methodology for the synthesis of skipped dienes using alkynes as latent alkenylmetal equivalents, we questioned whether a β-borylalkenylcopper intermediate could be generated catalytically and exploited in a Pd-catalyzed allylic substitution under synergistic catalysis (Scheme 1).[13-15] The combination of Cu and Pd catalysis would allow for concomitant activation of both the alkyne and the allyl substrate and provide total control over the different selectivity factors associated to this transformation, giving access to regio- and stereodefined skipped dienes bearing a Bpin group which can be further functionalized.

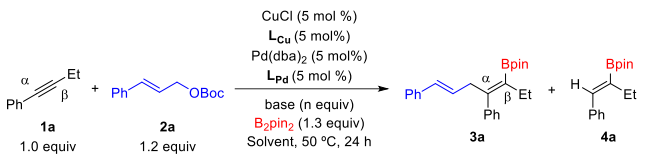
Scheme 1. Synthesis of borylated skipped dienes via Cu/Pd-catalyzed allylboration of alkynes



In our proposed dual catalytic mechanism (Scheme 1), a regio- and stereoselective borylcupration of the alkyne **1** with LCu-Bpin complex **II** would catalytically generate β-borylalkenylcopper(I) intermediate **III**. In the second catalytic cycle, a cationic π-allyl Pd(II) complex **V** would be formed by oxidative addition of an allyl substrate to a Pd(0) complex **IV**. Reaction between intermediates **III** and **V**, in which the palladium catalyst controls the regioselectivity of the allylic substitution,[16] would connect both cycles with formation of the borylated skipped diene **3** and regeneration of both catalysts **I** and **IV**. Besides the challenging control of the regio- and stereoselectivity, success of our proposed strategy also requires a high level of chemoselectivity as competitive addition of B_2pin_2 to the allyl substrate, which has been described to

proceed either under copper[17] and palladium[18] catalysis, has to be suppressed. Herein, we describe the successful implementation of this idea and thus the development of a three-component catalytic process which allows for the regio-, stereo- and chemoselective synthesis of borylated skipped dienes from readily available B_2pin_2 and a wide variety of alkynes and allylic carbonates. The reaction operates under relatively mild conditions and selectivity is governed by strict catalyst control.

Table 1. Optimization of the Synergistic Cu/Pd-Catalyzed Allylboration of Alkynes



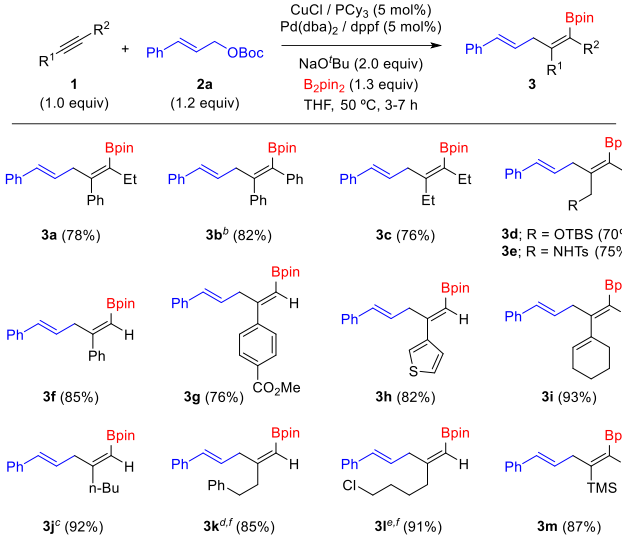
entry	solvent	base (n equiv)	L_{Cu}	L_{Pd}	Conv. (%)[a]	**3a**/**4a** (%)[a]
1[b]	toluene	NaO^{t}Bu (0.2)	PCy_3	dppe	11	8/3
2	toluene	NaO^{t}Bu (1.3)	PCy_3	dppe	67	49/18
3	THF	NaO^{t}Bu (1.3)	PCy_3	dppe	82	57/25
4	THF	NaO^{t}Bu (1.3)	PCy_3	dppf	>99	70/30
5	THF	NaO^{t}Bu (1.3)	IMes	dppf	70	45/25
6	THF	NaO^{t}Bu (1.3)	SIMes	dppf	traces	n.d.
7	THF	NaO^{t}Bu (1.3)	PPh_3	dppf	35	15/20
8	THF	NaO^{t}Bu (1.3)	L1	dppf	27	15/12
9	THF	NaO^{t}Bu (1.3)	L2	dppf	95	55/39
10	THF	LiO^{t}Bu (1.3)	PCy_3	dppf	41	34/7
11	THF	KO^{t}Bu (1.3)	PCy_3	dppf	58	41/17
12	THF	NaO^{t}Bu (2.0)	PCy_3	dppf	>99	94/6
13[c]	THF	NaO^{t}Bu (2.0)	PCy_3	dppf	>99	93/7

Reactions performed on a 0.2 mmol scale (0.1 M). α/β and S_N2/S_N2' >99:1 in all cases. [a]Determined by ^{1}H-NMR using Ph_3CH as internal standard. [b]10 mol% of both catalysts. [c]Cinnamyl methyl carbonate used instead of **2a**. dppe = 1,2-bis (diphenylphosphinoethane). dppf = 1,1'-bis(diphenylphosphinoferrocene). **L1** = P(*o*-tolyl)$_3$. **L2** = P(*p*-OMe-C_6H_4)$_3$. IMes = 1,3-dimesitylimidazolidinium chloride. SIMes = 1,3-bis(mesityl)imidazolium chloride. n.d. = not determined

At the outset of our investigation, we selected a reaction involving B_2pin_2, 1-phenyl-1-butyne (**1a**) and *tert*-butyl cinnamyl carbonate (**2a**) to evaluate both the feasibility and selectivity of the process (Table 1 and Supporting Information, Tables S1-S6). Initial experiments demonstrated that a stoichiometric amount of base is required to achieve good level of conversion (entries 1 and 2).[19] Remarkably, these preliminary results already showed the great selectivity of the proposed strategy as **3a** was obtained as a single isomer (out of the eight possible isomers arising from *syn* vs. *anti* borylcupration, α vs. β allylation of the alkyne and S_N2 vs. S_N2' allylic substitution), with the alkyne hydroboration product **4a** being the only side product. As hypothesized in our proposed mechanism, **3a** was the result of a *syn*-selective borylcupration and an α- and S_N2-selective allylation. Evaluation of different solvents (entries 2-3 and Table S1), palladium catalysts (entries 3-4 and Table S2), copper complexes (entries 4-9 and Table S3) and bases (entries 10-11 and Table S4) revealed that the combination of CuCl/PCy_3, Pd(dba)$_2$/dppf, NaO^{t}Bu in THF is the most efficient system for this transformation (entry 4). Moreover, an increase in the amount of NaO^{t}Bu (2.0 equiv) afforded **3a** in an excellent 94% NMR yield almost precluding the formation of **4a** (entry 12). Importantly, no formation of **3a** was observed in the absence of either copper or palladium catalysts (Table S6). As expected cinnamyl methyl carbonate provided comparable results to those obtained with **2a** under the optimized conditions (entry 13). On the other hand, cinnamyl phosphate, acetate and bromide were not efficient substrates for this transformation (Table S5).

Having established the optimized conditions for the Cu/Pd catalyzed allylboration of alkynes (Table 1, entry 12), we set out to investigate the scope of the reaction. First, we explored this new transformation by using different alkynes **1** (Table 2).

Table 2. Scope of alkynes[a]

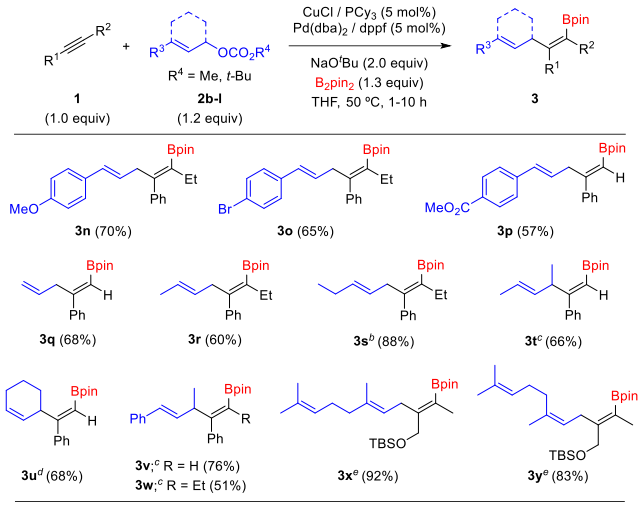


[a]Reactions performed on a 0.5 mmol scale. α/β and S_N2/S_N2' ratios >99:1 unless otherwise noted. Yields refer to isolated pure products. Regioselectivity determined by GC and ^{1}H-NMR analysis of the reaction crude. [b]Structure was confirmed by X-ray analysis. [c]α/β = 95:5. [d]α/β = 90:10. [e]α/β = 82:18. [f]Combined yield of both α and β regioisomers. For a list of alkynes **1**, see Supporting Information page S4.

Reactions proceeded with total stereo- and regioselectivity and furnished exclusively the corresponding dienes **3** in nearly all cases. Moreover, several functional groups such as silyloxy, sulfonamide, chloro, ester and trimethylsilyl groups were well tolerated. Internal alkynes bearing both aromatic or aliphatic substituents proved to be very efficient substrates affording the corresponding products **3a-e** in very good yields. Interestingly, dialkylalkynes **1d** and **1e** without a strong electronic bias[7d] to control the borylcupration step exhibited complete regioselectivity. Terminal alkynes were also efficient partners for this transformation despite the acidity of the terminal proton. Aryl and heteroaryl-substituted alkynes **1f-h** and enyne **1i** gave rise to the corresponding products **3f-i** in very good yields without any trace of the corresponding hydroboration products. Remarkably, alkyl-substituted terminal alkynes, which exhibited poor regioselectivity in copper-catalyzed allylboration[12] and alkylboration[8b] reactions, showed high levels of selectivity under our dual Cu/Pd catalytic conditions. Borylated diene **3j** was obtained from 1-hexyne with near perfect selectivity in 92% yield. The presence of a phenyl or a chloro group in the alkyl substituent caused a slight decrease on the α/β selectivity but products **3k** and **3l** were still obtained in good yields with perfect S_N2 selectivity. Noteworthy is the reaction with trimethylsilylacetylene[20] which gives stereoselective access to dienes (**3m**) featuring Bpin and TMS substituents which allow for further orthogonal functionalization of the diene.

Different allyl carbonates were evaluated under the standard conditions (Table 3).

Table 3. Scope of allyl substrates[a]

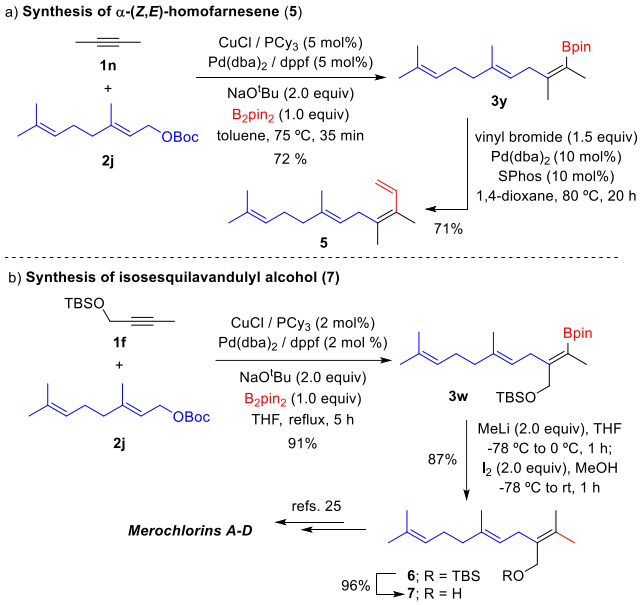


[a]Reactions performed on a 0.5 mmol scale. α/β and S_N2/S_N2' ratios >99:1 in all cases. Yields refer to isolated pure products. Regioselectivity determined by ^{1}H-NMR analysis of the reaction crude. [b]**(Z)-2g** used at 60 °C. [c]In toluene at 50 °C. [d]In toluene at 75 °C. [e]THF reflux using 1.1 equiv of B_2pin_2. For a list of alkynes **1** and allyl carbonates **2**, see Supporting Information page S4.

Both electron-rich and electron-deficient cinnamyl substrates worked well and afforded products **3n-p** in good yields with perfect α and S_N2 selectivity. Remarkably, in the case of **3o**, the catalytic system tolerated the presence of an aromatic bromide. There was no evidence of borylation of the aryl bromide[21] thus demonstrating the extremely high chemoselectivity of this dual catalytic system. Terminal and aliphatic allyl carbonates were also suitable substrates for this transformation showing good reactivity with both terminal and internal alkynes (**3q-s**). When (*Z*)-*tert*-butyl pent-2-en-1-yl carbonate **2g** was used, inversion of the configuration of the allyl double bond took place and the corresponding diene **3s** was obtained as pure (*Z,E*) isomer.[22] The reaction was also compatible with the use of secondary cyclic and acyclic allylic carbonates (**3t-w**) with toluene being the most efficient solvent in these cases. Interestingly, complete S_N2 selectivity was still observed in the formation of dienes **3v** and **3w** from unsymmetrical secondary allyl carbonate **2j**. The use of tri-substituted allylic carbonates was exemplified by using geraniol (**2k**) and nerol (**2l**) derivatives. In both cases the corresponding products **3x** and **3y** were obtained in excellent yield and with complete regio- and stereoselectivity and total retention of the configuration of the double bond of the starting allylic substrate.[23] These results show that synergistic Cu/Pd catalysis allows for an efficient allylboration of alkynes which features total S_N2-type regioselectivity enabled by the Pd catalytic cycle. This is in sharp contrast with the recently reported copper-catalyzed allylboration of alkynes with allyl phosphates[12] in which regioselectivity is governed by substrate control and formal S_N2 or S_N2' substitution products, or mixtures of both, are obtained depending on the nature of the alkyne and the allyl phosphate.

To illustrate the synthetic utility of the present catalytic methodology, we targeted the synthesis of two natural products (Scheme 2). *(Z,E)*-α-Homofarnesene **5**, a component of the trail pheromone of the fire-ant,[24] could be obtained in two steps via Cu/Pd-catalyzed allylboration of 2-butyne **1n** with allyl carbonate **2k** and subsequent Suzuki coupling with vinyl bromide (Scheme 2a). This new synthetic route reduces significantly the number of steps and provides a single stereoisomer in contrast to previous syntheses which afforded mixtures of the (*Z,E*) and (*E,E*) homofarnesenes.[24b,c]

Scheme 2. Synthetic applications



We also applied our methodology to the synthesis of isosesquilavandulyl alcohol **7** (Scheme 2b), a key intermediate in the synthesis of Merochlorins A-D which are marine meroterpenoid secondary metabolites with potent antibiotic activity.[25] Synthesis of **3x** was executed on larger scale (3 mmol) using a reduced catalyst loading (2 mol% of both copper and palladium catalysts) and still furnished the product without erosion of yield (92%). Conversion of the C-Bpin to a C-Me bond was performed by reaction with MeLi and iodine,[26] affording **6** in 87% yield. Final cleavage of the TBS group delivered isosesquilavandulyl alcohol **7** in 77% overall yield. This route not only gives straightforward access to **7** but also offers the possibility of synthesizing artificial analogs of Merochlorins by alternative functionalization (e.g. trifluoromethylation, fluorination) of the C-Bpin bond.

In summary, we have described a synergistic Cu/Pd-catalyzed three-component reaction of alkynes, B_2pin_2 and allyl carbonates. This transformation represents the first example of the use of catalytically generated β-boryl-alkenylcopper species in Pd-catalyzed allylic substitution. The reaction affords borylated skipped dienes from good to excellent yields with a remarkable regio-, stereo- and chemoselectivity. The synthetic potential of this method has been illustrated by the syntheses of naturally occurring *(Z,E)*-α-homofarnesene and isosesquilavandulyl alcohol from simple starting materials. Mechanistic studies, development of an enantioselective version and extension to related systems are in progress.

ASSOCIATED CONTENT

Supporting Information. List of substrates, optimization tables, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) As the use of allyl carbonate **2a** would facilitate the regeneration of LCuO^{t}Bu after the allylation event, the requirement of a stoichiometric amount of base might be due to the formation of a more reactive alkenylcuprate from alkenylcopper species **III** by reaction with NaO^{t}Bu. For a proposed alkenylcuprate intermediacy in copper-catalyzed carboboration reactions see refs. 6c and 8b.

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(22) Inversion of the allyl double bond configuration might arise from π-σ isomerization and C-C bond rotation of the allyl-Pd(II) intermediate.

(23) Stereochemical retention of the double bond geometry would be the result of a slow π-σ-π isomerization of the corresponding trisubstituted allyl-Pd(II) intermediate.

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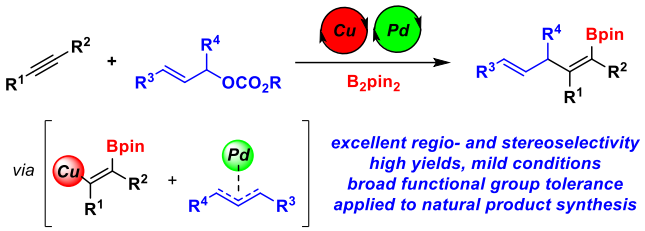
Cu
Pd
B2pin2
Bpin
via
excellent regio- and stereoselectivity
high yields, mild conditions
broad functional group tolerance
applied to natural product synthesis